Laboratory of Protozoology

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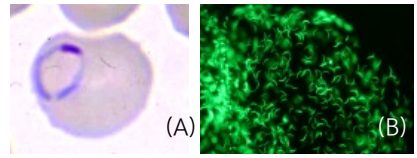
Malaria is one of the world's three major infectious diseases caused by Plasmodium species. Malaria parasite is an eukaryotic parasite that parasitizes the host body in a more diverse range of ways than viral or bacterial pathogens. Their parasitic strategies were established after a long evolutionary struggle with host and are beyond our imagination. We are interested in how parasitism is established through the interaction between molecules of parasites and host cells, including immune cells. We have developed our own genetic manipulation techniques, such as CRISPR/Cas, which can be used as tools, and are working to reveal the elegant parasitization strategies.

Development of Plasmodium artificial chromosomes and CRISPR/Cas9 system

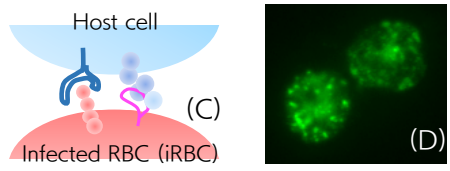
Genetic engineering technology for malaria parasite is essential for its molecular biological research. However, parasite has been known as one of the most difficult organisms to genetically manipulate due to its parasitism in host cells (erythrocytes), which makes gene transfer difficult, and the low efficiency of incorporating foreign genes into its chromosomes. On the other hand, we identified centromeres responsible for chromosome segregation based on parasite's genome information and succeeded in creating an artificial chromosome by combining telomere and replication origin with centromere. The artificial chromosome behaves like real chromosome within parasites and are maintained stably as they are equally distributed into daughter parasites, which enables efficient production of transgenic parasites. In addition, it has been found that under culture, the mature schizont degrades the erythrocyte membrane just before its egress and temporarily remains in the thin membrane, and by utilizing this phenomenon, highly efficient transfection method has been successfully developed. Furthermore, by mounting CRISPR/Cas9 on artificial chromosomes and combining it with the high-efficiency transfection method, we have succeeded in developing a method that dramatically improves the efficiency of foreign gene incorporation. It is now possible to produce recombinant parasites in about two weeks with an efficiency of more than 90%, thus solving a conventional technical limitation.

Interaction between surface antigens of infected erythrocyte and host receptors

Of human malaria parasites, P. falciparum causes the most severe symptoms in humans. During erythrocyte infection, P. falciparum transports to and presents its own proteins on the surface of infected erythrocytes. PfEMP1 and RIFIN have been identified as erythrocyte surface molecules. CD36, ICAM1 and EPCR on vascular endothelial cells have been identified as receptors for PfEMP1. P. falciparum binds to and embolisms cerebral vascular endothelium via binding of PfEMP1 to these molecules, causing severe coma and brain damage (cerebral malaria). Our collaborative work on RIFIN has also shown that LILRB1, an immunosuppressive receptor widely expressed on immune cells, is a receptor for RIFIN, and that parasite uses RIFN to suppress host immunity in favor of parasitization.Approximately 60 PfEMP1 genes and 150-200 RIFIN genes are encoded on the genome of P. falciparum. However, only ~20 surface antigens have been found to have a known function, while the rest remain unknown. We are currently analyzing the functions and host receptors of remained PfEMP1 and RIFINs comprehensively using new technologies such as Cas12-Ultra and Cas12k and artificial chromosome technology. Through these studies, we hope to elucidate the elegant parasitic strategies of parasites, leading to the development of vaccines and treatments for cerebral malaria.



(A) Red blood cell infected with P. falciparum
(B) GFP-expressed sporozites



(C) Image of Host-iRBC interaction
(D) IFA of Surface antigens on iRBCs

Basic biological research on infectious diseases can be based on academic interest and application. If you are interested in both of them, let's work on malaria research together with us!

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